REMARKS

In the Advisory Action of August 31, 2005, the Examiner asserted that Applicant's arguments require additional search and consideration. Applicants respectfully request reconsideration and allowance of claim 36 in view of the following remarks.

The Examiner maintained the rejection of claim 36 under 35 U.S.C. § 103(a) as being unpatentable over the Bersinger *et al.* reference (*Brit. J. Obstet. Gynaecol.*, 91:1245-1248 (1984)) in view of the Epstein *et al.* reference (*Proc. Natl. Acad. Sci. USA*, 89:10435-10439 (1992)), the Harlow and Lane reference (Antibodies: A Laboratory Manual, 1988, Cold Spring Harbor Laboratory, p. 313), and the Oxvig *et al.* reference (*J. Biol. Chem.*, 268:12243-12246 (1993)). Specifically, the Examiner stated that:

> Bersinger et al teach that a problem of interest is to determine whether PAPP-A levels differ during the proliferative and luteal phases of the menstrual cycle (pg 1247, parg 2). Oxvig et al teach that commercially available anti-PAPP-A antibodies previously used to determine PAPP-A levels react with MBP and probably with proMBP and that results based on the use of said antibodies must be questioned (pg 12246, parg 3). For a person of ordinary skill in the art, said teachings suggest that preparation of antibodies specific for PAPP-A, which don't cross-react with MBP, proMBP, or the PAPP-A/MBP complex, should be prepared and used to measure PAPP-A levels during the menstrual cycle. As described in the prior action, Epstein et al and Harlow et al teach how to make and purify highly specific antibodies by immunoaffinity purification methods.

Applicants respectfully disagree. The combination of cited art does not teach or suggest a method for detecting PAPP-A in a biological sample that includes contacting the biological sample with an antibody having specific binding affinity for PAPP-A, but not PAPP-A/pro major basic protein complex. In particular, the Oxvig *et al.* reference does not teach or suggest that PAPP-A can circulate in an uncomplexed form. Rather, the Oxvig *et al.* reference indicates that circulating PAPP-A is complexed with proMBP through disulfide bridge formation. In fact, the Oxvig *et al.* reference states on page 12243 that "[w]e conclude that circulating PAPP-A is a disulfide-bound complex between PAPP-A and proMBP" and on page 12245 that "[t]he conclusion that circulating PAPP-A is complexed with proMBP through disulfide bridge formation is based on the following concordant evidence." Thus, the Oxvig *et al.* reference provides no motivation for one of ordinary skill in the art to produce an antibody having specific

binding affinity for PAPP-A, but not PAPP-A/pro major basic protein complex. Merely pointing out that commercial anti-PAPP-A preparations react with MBP "and probably with proMBP" (Oxvig *et al.* at page 12246) falls far short of suggesting that a person having ordinary skill in the art should make or use the recited antibody.

It is only in view of the present specification that one of ordinary skill in the art would understand that an uncomplexed form of PAPP-A even exists. As indicated in Applicants' specification at page 6, lines 23-24, approximately 1% of PAPP-A in pregnancy plasma and serum is not complexed with proMBP protein and instead exists as a noncomplexed PAPP-A dimer. In addition, page 31, lines 19-30 of Applicants' specification indicates that proMBP dramatically inhibits the activity of PAPP-A in pregnancy serum by forming a covalent complex with PAPP-A. Measurable PAPP-A activity of pregnancy serum results from the fraction of uncomplexed PAPP-A. The cited art must be viewed without the benefit of impermissible hindsight vision afforded by Applicants' specification. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ('The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.')." *In re Dembiczak*, 174 F.3d 1308 (Fed. Cir. 1999).

In light of the above, Applicants request withdrawal of the rejection of claim 36 under 35 U.S.C. § 103(a).

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CONCLUSION

Applicants submit that claim 36 is in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 10/17/05

Monica McCormick Graham, Ph.D.
Reg. No. 42,600

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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